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Psychosocial Influences on Vaccine Responses

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Abstract

Interdisciplinary work between psychologists and immunologists has shown that factors like stress could be the trigger that lead to the development of a bout of illness. By studying the response to vaccination, we can examine immune function in the context of the rest of the body in a clinically meaningful way. This technique has been used to demonstrate consistent relationships between stress and the response to influenza vaccination and other vaccines, as well as links between other factors, such as social support and personality, and vaccination-induced protection against disease. There are several ways the vaccination response can be used to understand more about how stress influences immunity. In addition, specific types of stress and other factors that influence our immune response appear to differ across different populations, which emphasises the importance of taking a life course approach to studying these relationships.

Why study vaccination in the context of psychological factors?

There are many methods for examining the effects of psychological factors on immunity. However, a clinically relevant model which examines the impact of psychological factors on the integrated response of the immune system to a challenge in the context of the rest of the body is the antibody response to vaccination. Vaccines act as real immune system challenges, although they are altered in such a way so not to induce disease either by being inactivated or killed, or only a component of the actual pathogen, so are really 'imitation infections'. Therefore, by measuring the antibody levels in response to vaccination we can assess directly how well the immune system responds to infectious challenge. It is also clinically relevant, in that antibody levels are directly related to susceptibility and resistance to infectious disease.

The vaccination response involves the coordination of a wide variety of immune cells. Antigen (any foreign material, e.g. a bacteria or virus) is initially recognized and presented by professional antigen presenting cells. The antigen is then recognised by specific T cells (T-lymphocytes, so called as they mature in the thymus) which process and present the antigen to B-cells or B-lymphocytes, the antibody factories of the immune system; this is termed a thymus-dependent response. Some vaccine antigen types are also recognized by B-cells without the necessity for T-cell help, thus termed a thymus-independent response. When stimulated by an antigen, B-lymphocytes replicate and mature into short lived plasma cells which produce the earliest antibody or immunoglobulin, IgM. In a primary response to an antigen not previously encountered, the peak IgM response occurs around five days after vaccination. Interaction between activated T- and B-cells leads to the production of high affinity or very specific antibodies in bodily fluids: IgG (found mainly in the blood) and IgA (found mainly at mucosal surfaces, e.g. in saliva). This more specific response peaks around 28 days after vaccination. Other types of antibody include IgE (part of the allergic response) and IgD. IgG is particularly important, as being the most prolific antigen in the blood and a more specific match to the particular antigen makes it more effective at antigen elimination. Secondary antibody responses, in which the immune system has been previously exposed to the antigen, are more rapid and of

greater magnitude; this is because some activated T- and B-cells become long lived resting memory cells, remaining in the immune system ready to respond quickly to challenge with previously encountered antigens. Not all individuals react with a strong antibody response to vaccination, particularly older adults who are only protected against influenza disease in 30-50% of cases following vaccination (Allsup, Haycox, Regan, & Gosney, 2004; Goodwin, Viboud, & Simonsen, 2006; Nichol, Margolis, Wuorenma, & Von Sternberg, 1994; Patriarca, 1994). Further, the increase in vaccination availability has not been paralleled by decreased influenza-related mortality (Simonsen et al., 2005). As well as age, psychosocial factors, such as stress, may alter both the quantity and quality of antibody present at different times after immunization, meaning that individuals suffering higher levels of stress are more at risk of infectious disease.

This review will present an overview of the literature on the relationships between stress and the antibody response to vaccination, beginning with the most consistent association; the relationship between stress and influenza vaccine response. It will also discuss some of the issues surrounding vaccination studies, including: the types of stress examined, the timing of stress assessment, the types of vaccinations used, and the population studied. In addition, it will address the associations between other key psychological factors such as social support and personality. Finally, it will discuss the implications for future research including ways to improve the antibody response in certain populations.

Stress in vaccination studies

In studies of psychological stress and vaccination, stress is often assessed using either life events checklists or perceived stress measures. Life events checklists consist of a list of major and minor life events, e.g. bereavement, moving house, and usually require participants to indicate which have occurred during the past month or year (Brown & Harris, 1989). Some also ask participants to indicate how stressful each event was on a rating scale. Life events have been shown to predict a variety of important physical health outcomes, including infectious disease (Cohen, Tyrell, & Smith, 1991), and mortality, particularly in the context of little emotional

support (Rosengren, Orth-Gomer, Wedel, & Wilhelmsen, 1993). In contrast, perceived stress scales measure individuals' feelings about how stressful their lives are rather than the direct occurrence of events (Cohen, Kamarck, & Mermelstein, 1983). Thus these measures are more susceptible to subjective bias, so links to objective health outcomes, such as antibody response, tend to be more variable. Another common way of assessing stress in the context of vaccination is to examine antibody responses among those with a key chronic stressor versus a matched control group, for example, older adults caregiving for a spouse with dementia. The stress of caregiving has been shown to relate to poor health and mortality (Schulz & Beach, 1999).

Stress and influenza vaccination

The antibody response to the influenza vaccination has received considerable attention, particularly in undergraduate student and older caregiver samples. The influenza vaccination is a commonly utilised vaccine and consists of three components or strains, usually two A strains and one B strain, which change each year depending on the key circulating varieties. A recent meta-analysis of 13 studies of psychological stress and influenza vaccination concluded that there is a significant negative relationship between psychological stress and antibody titre following influenza vaccination (Pedersen, Zachariae, & Bovbjerg, 2009). These studies included five in caregivers and eight assessing the impact of stressful life events or perceived stress. The meta-analysis concluded that psychological stress, however measured, had a similar negative impact on influenza vaccine response, but that antibody responses to A/H1N1 and B-influenza types were more sensitive to the influence of stress (Pedersen, et al., 2009). However, it is difficult at this stage to explain why antibodies against influenza strains are differentially associated with stress. One possibility is that strain novelty influences the associations observed (Gulati, Keitel, & Air, 2007; Vedhara, Fox, & Wang, 1999), with more novel strains being more susceptible to stress effects.

The impact on certain A-strains and on B-strains is clearly shown in several studies of students. For example, those reporting higher stressful life event exposures and/or higher perceived stress

prior to vaccination showed poorer responses to the A-strains of the vaccine at five weeks (around the time of the peak response) and five months post-vaccination (indicating the decay in antibody response over time) (Burns, Carroll, Drayson, Whitham, & Ring, 2003). This was replicated for the numbers and severity of stressful life events prior to vaccination with the response to the B/Shangdong influenza strain at both five weeks and five months post-vaccination (Phillips, Burns, Carroll, Ring, & Drayson, 2005). Similarly, in a study of the effects of daily stress and feelings of being overwhelmed during the 10 days following vaccination, higher stress ratings were associated with lower antibody titres to the A/New Caledonia strain at both one and four months following vaccination (Miller et al., 2004). These studies provide evidence that stressful life events both preceding and in the period immediately following vaccination can influence the antibody response. They also show that both the peak antibody response at around four weeks and the decay in antibody protection over time are influenced by stressful life events,

Timing of stress assessment

This issue of the timing of stress assessment has been developed further in studies of different vaccinations including hepatitis B, which is useful in this context, as the vaccination schedule consists of three inoculations over a six month period. The largest of these studies examined the association between life events stress and the final antibody titre in students, vaccinated either in the past twelve months or at least thirteen months previously (Burns, Carroll, Ring, Harrison, & Drayson, 2002). Whereas life events exposure was not related to antibody response in the recently vaccinated cohort, participants in the earlier vaccinated cohort who reported higher life events over the past year were over twice as likely to show an inadequate antibody titre as those with lower life events exposure. This finding suggests that the immunogenicity, the ability to induce a strong vaccination response, of hepatitis B vaccination may initially override the influence of life events stress, although there was also more power to detect effects in the earlier vaccinated cohort as more participants exhibited inadequate antibody titres (Burns, et al., 2002). Nevertheless, this study provides some evidence that psychosocial stress in the period following

vaccination can have effects on the rate of deterioration of antibody protection (Burns, Carroll, Ring, & Drayson, 2003).

In a study where a low dose of hepatitis B vaccine was administered, a higher stress index, comprising life events exposure and psychological symptoms, measured at two months post-vaccination (thus considering the period post-vaccination) was associated with a poorer final six month antibody response, and the stress index at six months also tended to relate negatively to antibody response (Jabaaij et al., 1993). However, as only the final antibody titre was measured, it is difficult to determine whether, in this instance, stress predominantly influenced initial formation or maintenance of antibody levels. Also, the inclusion of psychological symptoms in the composite stress index makes it difficult to ascribe this finding to any specific aspect of stress (Burns, Carroll, Ring, et al., 2003). A similar study using the full dosage hepatitis B vaccination did not yield any significant stress effects (Jabaaij et al., 1996), although it is possible that this was due to the absence of a two-month assessment of stress, which was the main predictor of antibody response in the previous study by this group. In a study measuring perceived stress and anxiety during the vaccination period, i.e. post-vaccination, these were not associated with the final antibody response to hepatitis B (Glaser et al., 1992). Further, life events stress prior to vaccination and perceived stress at the time of the initial vaccination were not related to antibody status five months following the initial inoculation in a more recent study (Marsland, Cohen, Rabin, & Manuck, 2001). On the whole, this would suggest either that stress prior to vaccination is less detrimental to the antibody response than stress post-vaccination, or that it is difficult to observe stress effects early on with the full dose hepatitis B vaccination, due to its immunogenicity. Given the findings with the influenza vaccination and stress, this latter seems the more likely explanation.

In contrast, one study reported a positive association between perceived life event stress, depression and anxiety during the vaccination period and hepatitis B antibody status nine months following the initial vaccination (Petry, Weems, & Livingstone, 1991). This anomalous result

has been attributed to the relatively low levels of stress experienced by the participants in this study, suggesting that moderate levels of life change stress experienced *during* the initial stages of antibody formation may be beneficial to the antibody response, although high levels may be detrimental (Petry, et al., 1991). Such an interpretation receives support from animal research where moderate stress at the time of vaccination has been associated with an enhanced antibody response (see e.g. (Dhabhar & McEwen, 1996).

Intensity and chronicity of stress and the vaccination response

Following on from the discussion above, such that moderate or less severe stress at the time of vaccination might actually have a beneficial effect, it has been suggested in recent years that acute (minutes or hours) stress may be immune enhancing when experienced close to the immune challenge. Such immune enhancement by acute stress would be an adaptive mechanism, and might be regarded as an integral component of the fight or flight response, and circumstances that elicit such a response are likely to also involve exposure to antigens and, therefore, a robust immune response would be adaptive for survival (Dhabhar & McEwen, 1996). Recently, our laboratory examined the effect of acute psychological stress on antibody response to vaccination in humans. Participants completed a 45 min time pressured, socially evaluated mental arithmetic task, or a resting control period, immediately prior to influenza vaccination. An enhancement of the antibody response to one of the influenza viral strains was found in women in the psychological stress group compared to control (Edwards et al., 2006).

Different types of vaccinations

Primary and secondary vaccinations

As indicated above, vaccination with an antigen to which the participant has not been previously exposed induces a primary antibody response whereas vaccination against more common pathogens such as influenza, induce a secondary immune response. By examining the effect of

stress on both primary and secondary immune responses, we can begin to determine which aspects of the immune response are most susceptible to stress-induced modulation.

Hepatitis B vaccination has been used in this context due to the vaccination schedule and the low likelihood of prior naturalistic exposure to this pathogen. In an earlier study, individuals reporting higher mean perceived stress and anxiety over the vaccination period were less likely to have sero-converted (produced a protective antibody level) by the time of the second inoculation (Glaser, et al., 1992). Whereas, an emotional disclosure intervention group did not differ from controls in antibody levels at the time of the second inoculation (Petrie, Booth, Pennebaker, Davison, & Thomas, 1995). However, psychological stress levels were not measured, making it difficult to interpret these data. More recently, we have used hepatitis A as a primary antigen. Students who reported a higher number and severity of life events had a poorer antibody response to hepatitis A at the 18-week, but not 4-week, follow-up, suggesting stress can impact upon the maintenance of antibody levels (Gallagher, Phillips, Ferraro, Drayson, & Carroll, 2008a). Early studies using the vaccination model used novel non-pathogenic antigens to examine the antigen-specific antibody response. Keyhole limpet hemocyanin (KLH), a protein, has been used in this context; the KLH-specific IgG antibody response was lower at eight weeks, but not three weeks, post-vaccination in participants reporting fewer positive life events prior to vaccination (Snyder, Roghmann, & Sigal, 1990).

The consensus of this evidence suggests that stress can influence the primary antibody response, particularly the maintenance of responses to novel antigens. It also supports the idea that life events stress effects are more likely to be evident with novel vaccine types (Phillips, Burns, et al., 2005). As discussed above, the secondary antibody response to hepatitis B vaccination has produced mixed results, but there appears to be stronger evidence for a negative effect of psychological stress on the secondary response to this antigen (Burns, Carroll, Ring, et al., 2003; Cohen, Miller, & Rabin, 2001), in line with the findings for the influenza vaccine.

Thymus-dependent and independent vaccinations

A further advantage to the vaccination model is that there are different types of vaccination, which can be used to help elucidate which cells involved in the vaccination response are influenced by psychological factors. Most vaccinations, which consist of inactivated or dead viruses like influenza, induce a thymus-dependent antibody response, as described above. A few vaccinations, however, protect against bacterial infections or toxins like meningococcal A or tetanus, respectively, which do not require T-cell help. There are also conjugate vaccines, in which substances that elicit a T-cell response are conjugated to a thymus-independent pathogen, such as a protein, in order to boost the efficiency of the antibody response against the thymus-independent pathogen. If psychological factors are consistently associated with the response to thymus-dependent and conjugate vaccinations but not with thymus-independent response, this would imply that it is T-cells that are particularly liable to psychological influence.

Indeed, there is evidence to suggest that stress may exert its effects mainly on T-cells; we showed that higher frequency and intensity of stressful life events were associated with a poorer response to influenza and meningococcal C (following previous conjugate meningococcal C vaccination), but not to thymus-independent meningococcal A (Phillips, Burns, et al., 2005). Similarly, no association was found between stress and antibody response to a thymus-independent pneumonia vaccination in pre-school children (Boyce et al., 1995). However, as older care-givers have been reported to show poorer maintenance of antibody levels over time following pneumonia vaccination than controls (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000), it is possible that other factors such as age and severity of stress may interact to impair antibody-mediated immunity more generally than just the T-cell response.

It should be noted that in the study of caregivers and the pneumonia vaccination, perceived stress did not differ between the caregiver and controls, but there was a significant difference in social support. This might suggest that thymus-dependent vaccinations are susceptible to the effects of stressful life events, but that thymus-independent vaccinations are more vulnerable to other

psychosocial factors such as lower social support. There is some evidence for this suggestion. In our own laboratory, we found that social support, but not life events stress, was positively associated with the response to a thymus-independent pneumococcal vaccine in young healthy students (Gallagher, Phillips, et al., 2008a; Gallagher, Phillips, Ferraro, Drayson, & Carroll, 2008b).

The comparison between thymus-dependent and –independent vaccination responses suggest that both types of response are susceptible to psychosocial influence, but that there are key variables which influence whether an effect on vaccination response is observed. These include: the type of psychosocial factor studied (i.e. stress versus social support), and the age of the population sampled. This article will now address each of these issues in turn.

Other psychosocial factors and vaccination

Social support

The support of friends and loved ones is an important determinant of immune health. Studies have assessed both functional social support, a measure of the quality and availability of social resources a person has, and structural social support, the number of friends a person can call on, in the context of vaccination. First, students reporting greater social support demonstrated a stronger combined immune response to the third inoculation of the three-dose hepatitis B vaccination (Glaser, et al., 1992). Second, loneliness and smaller social network size were associated with a poorer antibody response to the A/New Caledonian strain of the influenza vaccination in college students (Pressman et al., 2005). Third, students with greater functional social support showed higher titres to the A/Panama influenza strain at both five weeks and five months following vaccination (Phillips, Burns, et al., 2005). In older nursing home residents, social support was also negatively correlated with pre- and post-vaccination titres against the A/Panama influenza strain yet positively with pre-vaccination antibody titres against the A/New Caledonia strain (Moynihan et al., 2004), a finding which even the authors were unable to

explain. Along with the caregiver study discussed above, these studies generally show that a lack of social support has a strong negative impact on antibody levels following vaccination.

Marriage is also a source of social support. In our own work, older adults who were married, and particularly those who were happily married, showed a better antibody response to the influenza vaccination than those who were unmarried or less happily married (Phillips et al., 2006). However, more general functional social support and social network size was not associated with antibody response in this older population (Phillips, et al., 2006). These findings perhaps lend weight to the suggestion that the population studied influences which psychosocial factors are important for the vaccination response. The impact of age will be further discussed later in this article.

Personality

Personality factors, although often examined in the context of health outcomes (see e.g., (Smith, Glaser, Ruiz, & Gallo, 2004) have scarcely been investigated relative to the vaccination response. First, among a group of 12-year old girls, those characterized by higher internalizing scores and lower self-esteem at baseline exhibited lower antibody titres following rubella vaccination (Morag, Morag, Reichenberg, Lerer, & Yirmiya, 1999). A similar concept, neuroticism, was negatively associated with both the peak antibody response to the A/Panama strain of an influenza vaccination, and the maintenance of antibody titres to this strain in students (Phillips, Carroll, Burns, & Drayson, 2005). Among female graduate students, trait negative affect/mood was negatively associated with the antibody response to the second hepatitis B injection (Marsland, et al., 2001). Further, independently of negative affect, trait positive affect was associated with a better antibody response following a second hepatitis B vaccination in graduate students (Marsland, Cohen, Rabin, & Manuck, 2006). Thus, both negative and positive traits appear to be able to influence this aspect of immune function and disease protection. However, in exercising and sedentary elderly individuals, dispositional optimism was not found to be associated with antibody titres following influenza vaccination (Kohut, Cooper, Nickolaus, Russell, & Cunnick, 2002). Inconsistencies in these results could be attributable to the different

measures of personality studied, or the different ages of the populations used, which will now be discussed in more detail.

Vaccination response in older adults

It is important to study the psychological influences on the antibody response to vaccination in older adults, given that they have less efficient immune systems due to immune ageing, which contributes to increased infectious disease susceptibility (Ginaldi, Loreto, Corsi, Modesti, & De Martinis, 2001). Further, it is possible that ageing of the immune system and stress interact such that stress takes its greatest toll on immunity in those who have existing immunosenescence (Graham, Christian, & Kiecolt-Glaser, 2006; Phillips, Burns, & Lord, 2007).

Caregiving

The vaccination response in older adults has mainly been considered in the context of the chronic stress of caregiving for a spouse with dementia. Studies have shown that caregivers have poorer antibody responses to vaccination in comparison to matched control participants (Glaser, et al., 1992; Glaser, et al., 2000; Vedhara et al., 1999). Similarly, caregivers who exhibited repetitive negative thoughts about their situation had lower antibody titres following influenza vaccination (Segerstrom, Schipper, & Greenberg, 2008). However, in younger populations, such as Multiple Sclerosis spousal caregivers, there was no difference in antibody response to influenza vaccination between caregivers and controls (Vedhara et al., 2002). This raises the issue of whether the poor antibody response observed in older caregivers is, to an extent, a function of an interaction between chronic stress exposure and immunosenescence (Graham, et al., 2006). A recent study from our group supports such a notion. Secretion rates of secretory immunoglobulin-A (S-IgA), a salivary antibody, were found to be lower in non-routine caregivers relative to controls, but only for the oldest (aged 63 years) of three distinct age cohorts (Gallagher et al., 2008).

There is an alternative explanation for the discrepancy in outcomes among the caregiver vaccination studies. Rather than immune ageing, perhaps it is the intensity of the stress experienced that determines whether caregiving becomes an issue for immunity (Vedhara, et al., 2002). Dementia is a disease characterised by much more severe cognitive and behavioural disturbances than multiple sclerosis (Gregory & Hodges, 1996; Keegan & Noseworthy, 2002; Neary et al., 1998; Poser et al., 1983), and older spousal caregivers of dementia patients have been found to report greater distress than younger multiple sclerosis caregivers (Vedhara, et al., 2002). Further, the results of two recent meta-analyses indicate that caregivers of dementia patients generally experience greater burden and report more symptoms of depression than those caring for non-dementia, e.g., cancer, patients, (Pinquart & Sorensen, 2003a, 2003b). Thus, it might be hypothesized that, irrespective of the caregiver's age, caring for someone with severe cognitive and behavioural problems will compromise immunity.

We have been able to test this hypothesis recently using a caregiving model in younger adults; young parents caring for children with developmental disabilities. Dealing with severe cognitive difficulties and behaviours that are problematic and distressing are the main challenges of such caring (Floyd & Gallagher, 1997; Hastings, Daley, Burns, & Beck, 2006; Higgins, Bailey, & Pearce, 2005; Maes, Broekman, Dosen, & Nauts, 2003). In our own studies of 30 caregivers for a child with a developmental disability (mainly Autism) versus matched controls, we have demonstrated that caregivers report high levels of stress, anxiety, depression, child problem behaviours, and low levels of social support. These caregivers also exhibited a poorer antibody response to a pneumonia vaccination than parents caring for typically developing children at both one and six months post-vaccination (Gallagher, Phillips, Drayson, & Carroll, 2009). Of the psychological variables considered, child problem behaviours mediated this effect. In addition, within the caregivers, parents reporting more child conduct problems, a component of the child problem behaviour measure, mounted a poorer antibody response at 1-month than parents reporting less conduct problems (Gallagher, Phillips, Drayson, & Carroll, 2009). Similarly, these parents mounted a poorer antibody

response to the B/Malaysia strain of an influenza vaccine at one and six months post-vaccination, which again appeared to be mediated by differences in child problem behaviours (Gallagher, Phillips, Drayson, & Carroll., 2009).

These recent findings in younger caregivers reinforce the hypothesis that an ageing immune system is not a pre-requisite for a poor response to medical vaccination in caregivers. Nevertheless, among our parental caregivers, older caregivers tended to have a poorer antibody response to B/Malaysia at 1-month, suggesting that we cannot dismiss the hypothesis that chronic stress and immunosenescence may have synergistic effects (Graham, et al., 2006).

Life events stress in older adults

Caregiving is a very specific stressor, and care-givers are likely to differ from the general population in ways other than the stress of care-giving, for example, in the amount of social support they receive. Research examining the impact of more general psychological stress on antibody levels following vaccination is sparse. However, it is important to study older adults in this context as they are likely to have different stress exposure histories than younger samples (Carroll, Phillips, Ring, Der, & Hunt, 2005) as well as immune ageing (Ginaldi, et al., 2001). One study found that older adults reporting higher perceived stress had lower antibody levels following influenza vaccination (Kohut, et al., 2002). As the baseline antibody level prior to vaccination was not known, however, the impact on the actual response to the vaccine could not be assessed. Similarly, nursing home residents who reported higher levels of perceived stress had lower pre-vaccine antibody titres to two influenza vaccine components (Moynihan, et al., 2004). However, it is not clear what this means, given that pre-vaccine titres could reflect differences in prior vaccine history or exposure. More recently, we observed that the stress of bereavement in the year prior to influenza vaccination was associated with a poorer antibody response to two of the influenza strains in a community sample of 184 adults aged 65 and over (Phillips, et al., 2006). Although overall negative life events exposure was not associated with vaccine response in this study, the effect found for bereavement suggests that stress is related to

pervasive immune effects throughout the life course, although what constitutes life events stress will vary depending on the age of the sample studied.

Future Directions

The studies reviewed above show the strong associations between psychological stress, other psychosocial factors and the immune response to vaccination, such that stressful psychological circumstances are associated with poorer antibody responses, while positive factors such as social support relate to a better immune response to vaccination. These findings suggest two main directions for future research. First, despite the range of vaccinations used in such studies, as yet little is known about the exact mechanisms by which stress and other factors can influence antibody responses to vaccination. Research incorporating a range of measurements, such as stress hormones, immune system messengers (cytokines), and the function of key cells in the vaccination response, such as antigen presenting cells, would be necessary to further our understanding regarding exactly how stress gets inside the body to affect this clinically relevant immune outcome. Second, the clinical implications, in terms of susceptibility to disease, arising from a better understanding of the relationships between psychological factors and the vaccination response are important, particularly in the context of older adults who already display poor vaccination responses. Psychological interventions to improve vaccination response in these populations could include techniques such as stress management, relaxation, cognitive behavioural therapy, and emotional disclosure.

One study showed an improvement in the ability of older caregivers for a spouse with dementia to mount a four-fold increase in antibody titre following influenza vaccination relative to matched controls, although the mechanisms of effect were unclear and the intervention group were not randomly sampled (Vedhara et al., 2003). Similarly, participants taking part in a written emotional disclosure intervention, where they wrote about their emotions about a previously undisclosed stressful event, showed significantly higher antibody titres at four and six months following vaccination with hepatitis B compared to a control non-intervention group

(Petrie, et al., 1995). A different clinical application of the vaccination model has arisen from the positive immune effects demonstrated in response to acute stress (Edwards, et al., 2006). These preliminary findings suggest that the development of such a behavioural challenge that could be applied in General Practitioner settings could be a way forward for improving the vaccination response. This would be particularly important for groups at risk of infectious disease such as older adults, the bereaved, and care-givers. At this stage, more work is required to establish exactly what types of intervention in which age groups and are likely to be the most beneficial for psychological, and hence immunological, health.

Conclusion

In conclusion, vaccination has had a substantial impact on public health, although not everyone mounts a satisfactory and protective antibody response to vaccination. This increasingly appears to be the case with progressing age. Studying antibody responses to vaccination is now contributing to the understanding of how psychosocial exposures can influence immunity and, consequently, resistance to disease. The current challenges are to unravel the underlying mechanisms and to develop and apply feasible behavioural interventions to boost the response to vaccination and, thus, optimize our resistance against infectious disease.

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References

- Allsup, S., Haycox, A., Regan, M., & Gosney, M. (2004). Is influenza vaccination cost effective for healthy people between ages 65 and 74 years? A randomised controlled trial. *Vaccine*, 23, 639-645.
- Boyce, W. T., Adams, S., Tschann, J. M., Cohen, F., Wara, D., & Gunnar, M. R. (1995). Adrenocortical and behavioral predictors of immune response to starting school. *Pediatric Research*, 38, 1009-1017.
- Brown, G. W., & Harris, T. O. (1989). *Social Origins of Depression: A study of psychiatric disorder in women*. London: Routledge.
- Burns, V. E., Carroll, D., Drayson, M., Whitham, M., & Ring, C. (2003). Life events, perceived stress and antibody response to influenza vaccination in young healthy adults. *Journal of Psychosomatic Research*, 55, 569-572.
- Burns, V. E., Carroll, D., Ring, C., & Drayson, M. (2003). Antibody response to vaccination and psychosocial stress in humans: relationship and mechanisms. *Vaccine*, 21, 2523-2534.
- Burns, V. E., Carroll, D., Ring, C., Harrison, L. K., & Drayson, M. (2002). Stress, coping and hepatitis B antibody status. *Psychosomatic Medicine*, 64, 287-293.
- Carroll, D., Phillips, A. C., Ring, C., Der, G., & Hunt, K. (2005). Life events and hemodynamic stress reactivity in the middle-aged and elderly. *Psychophysiology*, 42, 269-276.
- Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, 24, 385-396.
- Cohen, S., Miller, G. E., & Rabin, B. S. (2001). Psychological Stress and Antibody Response to Immunization: A Critical Review of the Human Literature. *Psychosomatic Medicine*, 63, 7-18.
- Cohen, S., Tyrell, D. A. J., & Smith, A. P. (1991). Psychological stress and susceptibility to the common cold. *The New England Journal of Medicine*, 325, 606-612.
- Dhabhar, F. S., & McEwen, B. S. (1996). Stress-induced enhancement of antigen-specific cell-mediated immunity. *J Immunol*, 156, 2608-2615.

- Edwards, K. M., Burns, V. E., Reynolds, T., Carroll, D., Drayson, M., & Ring, C. (2006). Acute stress exposure prior to influenza vaccination enhances antibody response in women. *Brain, Behavior and Immunity*, 20, 159-168.
- Floyd, F. J., & Gallagher, E. M. (1997). Parental stress, care demands, and use of support services for school-age children with disabilities and behavior problems. *Family Relations*, 46, 359-371.
- Gallagher, S., Phillips, A. C., Drayson, M. T., & Carroll, D. (2009). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346.
- Gallagher, S., Phillips, A. C., Drayson, M. T., & Carroll, D. (2009). Care-giving for a child with intellectual disabilities is associated with a poor antibody response to influenza vaccination. *Psychosomatic Medicine*, 71, 341-344.
- Gallagher, S., Phillips, A. C., Evans, P., Der, G., Hunt, K., & Carroll, D. (2008). Caregiving is associated with low secretion rates of immunoglobulin A in saliva. *Brain Behav Immun*, 22, 565-572.
- Gallagher, S., Phillips, A. C., Ferraro, A. J., Drayson, M. T., & Carroll, D. (2008a). Psychosocial factors are associated with the antibody response to both thymus-dependent and thymus-independent vaccines. *Brain Behav Immun*, 22, 456-460.
- Gallagher, S., Phillips, A. C., Ferraro, A. J., Drayson, M. T., & Carroll, D. (2008b). Social support is positively associated with the immunoglobulin M response to vaccination with pneumococcal polysaccharides. *Biol Psychol*, 78, 211-215.
- Ginaldi, L., Loreto, M. F., Corsi, M. P., Modesti, M., & De Martinis, M. (2001). Immunosenescence and infectious diseases. *Microbes Infect*, 3, 851-857.
- Glaser, R., Kiecolt-Glaser, J. K., Bonneau, R. H., Malarkey, W., Kennedy, S., & Hughes, J. (1992). Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. *Psychosomatic Medicine*, 54, 22-29.
- Glaser, R., Sheridan, J. F., Malarkey, W., MacCallum, R. C., & Kiecolt-Glaser, J. K. (2000). Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. *Psychosomatic Medicine*, 62, 804-807.

- Goodwin, K., Viboud, C., & Simonsen, L. (2006). Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine*, 24, 1159-1169.
- Graham, J. E., Christian, L. M., & Kiecolt-Glaser, J. K. (2006). Stress, age, and immune function: toward a lifespan approach. *Journal of Behavioral Medicine*, 29, 389-400.
- Gregory, C. A., & Hodges, J. R. (1996). Clinical features of frontal lobe dementia in comparison to Alzheimer's disease. *J Neural Transm Suppl*, 47, 103-123.
- Gulati, U., Keitel, W. A., & Air, G. M. (2007). Increased antibodies against unfolded viral antigens in the elderly after influenza vaccination. *Influenza Other Respi Viruses*, 1, 147-156.
- Hastings, R. P., Daley, D., Burns, C., & Beck, A. (2006). Maternal distress and expressed emotion: cross-sectional and longitudinal relationships with behavior problems of children with intellectual disabilities. *American Journal of Mental Retardation*, 111, 48-61.
- Higgins, D. J., Bailey, S. R., & Pearce, J. C. (2005). Factors associated with functioning style and coping strategies of families with a child with an autism spectrum disorder. *Autism*, 9, 125-137.
- Jabaaij, L., Grosheide, P. M., Heijtkink, R. A., Duivenvoorden, H. J., Ballieux, R. E., & Vingerhoets, A. J. J. M. (1993). Influence of perceived psychological stress and distress on antibody response to low dose rDNA hepatitis B vaccine. *Journal of Psychosomatic Research*, 37, 361-369.
- Jabaaij, L., Van Hattum, J., Vingerhoets, A. J. J. M., Oostveen, F. G., Duivenvoorden, H. J., & Ballieux, R. E. (1996). Modulation of immune response to rDNA hepatitis B vaccination by psychological stress. *Journal of Psychosomatic Research*, 41, 129-137.
- Keegan, B. M., & Noseworthy, J. H. (2002). Multiple sclerosis. *Annu Rev Med*, 53, 285-302.
- Kohut, M. L., Cooper, M. M., Nickolaus, M. S., Russell, D. R., & Cunnick, J. E. (2002). Exercise and psychosocial factors modulate immunity to influenza vaccine in elderly individuals. *Journal of Gerontology*, 57, 557-562.
- Maes, B., Broekman, T. G., Dosen, A., & Nauts, J. (2003). Caregiving burden of families looking after persons with intellectual disability and behavioural or psychiatric problems. *J Intellect Disabil Res*, 47, 447-455.

- Marsland, A. L., Cohen, S., Rabin, B. S., & Manuck, S. B. (2001). Associations between stress, trait negative affect, acute immune reactivity, and antibody response to hepatitis B injection in healthy young adults. *Health Psychology*, 20, 4-11.
- Marsland, A. L., Cohen, S., Rabin, B. S., & Manuck, S. B. (2006). Trait positive affect and antibody response to hepatitis B vaccination. *Brain Behav Immun*, 20, 261-269.
- Miller, G. E., Cohen, S., Pressman, S., Barkin, A., Rabin, B. S., & Treanor, J. J. (2004). Psychological stress and antibody response to influenza vaccination: when is the critical period for stress, and how does it get inside the body? *Psychosomatic Medicine*, 66, 215-223.
- Morag, M., Morag, A., Reichenberg, M. A., Lerer, B., & Yirmiya, R. (1999). Psychological variables as predictors of rubella antibody titers and fatigue - a prospective double blind study. *Journal of Psychiatric Research*, 33, 389-395.
- Moynihan, J. A., Larson, M. R., Treanor, J., Duberstein, P. R., Power, A., Shore, B., et al. (2004). Psychosocial factors and the response to influenza vaccination in older adults. *Psychosom Med*, 66, 950-953.
- Neary, D., Snowden, J. S., Gustafson, L., Passant, U., Stuss, D., Black, S., et al. (1998). Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*, 51, 1546-1554.
- Nichol, K. L., Margolis, K. L., Wuorenma, J., & Von Sternberg, T. (1994). The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *The New England Journal of Medicine*, 331, 778-784.
- Pariente, C. M., Carpinello, B., Orru, M. G., Sitzia, R., Piras, A., Farci, A. M., et al. (1997). Chronic caregiving stress alters peripheral blood immune parameters: the role of age and severity of stress. *Psychotherapy and Psychosomatics*, 66, 199-207.
- Patriarca, P. A. (1994). Editorial: A randomized controlled trial of influenza vaccine in the elderly: Scientific scrutiny and ethical responsibility. *JAMA*, 272, 1700-1701.
- Pedersen, A. F., Zachariae, R., & Bovbjerg, D. H. (2009). Psychological stress and antibody response to influenza vaccination: a meta-analysis. *Brain Behav Immun*, 23, 427-433.

Petrie, K. J., Booth, R. J., Pennebaker, J. W., Davison, K. P., & Thomas, M. G. (1995).

Disclosure of trauma and immune response to a hepatitis B vaccination program. *Journal of Consulting and Clinical Psychology*, 63, 787-792.

Petry, J., Weems, L. B., & Livingstone, J. N. I. (1991). Relationship of stress, distress, and the immunologic response to a recombinant hepatitis B vaccine. *Journal of Family Practice*, 32, 481-486.

Phillips, A. C., Burns, V. E., Carroll, D., Ring, C., & Drayson, M. (2005). The association between life events, social support and antibody status following thymus-dependent and thymus-independent vaccinations in healthy young adults. *Brain, Behaviour and Immunity*, 19, 325-333.

Phillips, A. C., Burns, V. E., & Lord, J. M. (2007). Stress and exercise: getting the balance right for an ageing immune system. *Exercise and Sports Sciences Reviews*, 35, 35-39.

Phillips, A. C., Carroll, D., Burns, V. E., & Drayson, M. (2005). Neuroticism, cortisol reactivity, and antibody response to vaccination. *Psychophysiology*, 42, 232-238.

Phillips, A. C., Carroll, D., Burns, V. E., Ring, C., Macleod, J., & Drayson, M. (2006).

Bereavement and marriage are associated with antibody response to influenza vaccination in the elderly. *Brain, Behavior and Immunity*, 20, 279-289.

Pinquart, M., & Sorensen, S. (2003a). Associations of stressors and uplifts of caregiving with caregiver burden and depressive mood: a meta-analysis. *J Gerontol B Psychol Sci Soc Sci*, 58, P112-128.

Pinquart, M., & Sorensen, S. (2003b). Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis. *Psychology and Aging*, 18, 250-267.

Poser, C. M., Paty, D. W., Scheinberg, L., McDonald, W. I., Davis, F. A., Ebers, G. C., et al. (1983). New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol*, 13, 227-231.

Pressman, S. D., Cohen, S., Miller, G. E., Barkin, A., Rabin, B. S., & Treanor, J. J. (2005).

Loneliness, social network size, and immune response to influenza vaccination in college freshmen. *Health Psychol*, 24, 297-306.

- Rosengren, A., Orth-Gomer, K., Wedel, H., & Wilhelmsen, L. (1993). Stressful life events, social support, and mortality in men born in 1933. *British Medical Journal*, 307, 1102-1105.
- Schulz, R., & Beach, S. R. (1999). Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *Jama*, 282, 2215-2219.
- Segerstrom, S. C., Schipper, L. J., & Greenberg, R. N. (2008). Caregiving, repetitive thought, and immune response to vaccination in older adults. *Brain Behav Immun*, 22, 744-752.
- Simonsen, L., Reichert, T. A., Viboud, C., Blackwelder, W. C., Taylor, R. J., & Miller, M. A. (2005). Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med*, 165, 265-272.
- Smith, T. W., Glaser, K., Ruiz, J. M., & Gallo, L. C. (2004). Hostility, anger, aggressiveness, and coronary heart disease: an interpersonal perspective on personality, emotion, and health. *J Pers*, 72, 1217-1270.
- Snyder, B. K., Roghmann, K. J., & Sigal, L. H. (1990). Effect of stress and other biopsychosocial factors on primary antibody response. *Journal of Adolescent Health Care*, 11, 472-479.
- Stetler, C., Chen, E., & Miller, G. E. (2006). Written disclosure of experiences with racial discrimination and antibody response to an influenza vaccine. *International Journal of Behavioral Medicine*, 13, 60-68.
- Vedhara, K., Bennett, P. D., Clark, S., Lightman, S. L., Shaw, S., Perks, P., et al. (2003). Enhancement of antibody responses to influenza vaccination in the elderly following a cognitive-behavioural stress management intervention. *Psychother Psychosom*, 72, 245-252.
- Vedhara, K., Cox, N. K., Wilcock, G. K., Perks, P., Hunt, M., Anderson, S., et al. (1999). Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. *Lancet*, 353, 627-631.
- Vedhara, K., Fox, J. D., & Wang, E. C. Y. (1999). The measurement of stress-related immune dysfunction in psychoneuroimmunology. *Neuroscience and Biobehavioural Reviews*, 23, 699-715.

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Vedhara, K., McDermott, M. P., Evans, T. G., Treanor, J. J., Plummer, S., Tallon, D., et al. (2002). Chronic stress in non-elderly caregivers: psychological, endocrine and immune implications. *Journal of Psychosomatic Research*, 53, 1153-1161.